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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/551,401 | 03/30/2006 | Paul Tardi | 532552001000 | 5586 |
| 25225 | 7590 | 11/17/2009 | EXAMINER | |
| MORRISON & FOERSTER LLP | | | KISHORE, GOLLAMUDI S | |
| 12531 HIGH BLUFF DRIVE | | | | |
| SUITE 100 | | | ART UNIT | PAPER NUMBER |
| SAN DIEGO, CA 92130-2040 | | | 1612 | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/551,401 | TARDI ET AL. | |
| | Examiner | Art Unit | |
| | GOLLAMUDI S. KISHORE | 1612 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 12 August 2009.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 42-46 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 42-46 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>1-10-06</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Claims included in the prosecution are 42-46.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 42-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Englom (British Journal of Cancer, 79 (2), 1999) or Kano (leukemia Research, vol. 17, 1993) or Guichard (Biochemical Pharmacology, vol. 55, 1998) in combination with applicant's statements of prior art record, in further combination with Vaage (Int. J. Cancer 1993), Saxon (Journal of Liposome Research) Bally (5,736,155) individually or in combination.

Englom teaches additive and supra-additive cytotoxicity of cisplatin-taxane combination in ovarian carcinoma cell lines (Summary).

Kano teaches synergistic effects of carboplatin in combination with cytosine arabinoside, mitoxantrone and CPT-11 (Irinotecan) and additive effects of carboplatin in combination with bleomycin, daunorubicin, etoposide and others in human leukemia cell lines (abstract).

Guichard discloses synergistic activity of 5-fluoracil and Irinotecan in human colorectal carcinoma cell line (abstract).

In essence, these references teach the synergistic effect of drug combinations.

What is lacking in these references are the use of various algorithms and analysis of the data using Chou-Talalay median-effect method and the use of liposomes as carriers.

Applicant on pages 20 and 21 state that various algorithm methods, Chou-Talalay median effect method to determine the synergistic activity of anti-cancer drugs is known in the art.

Vaage et al teach compositions containing liposomes (vehicles) and encapsulated therein two therapeutic agents, vincristine and doxorubicin. The liposome sizes are 80 nm. According to Vaage, the liposome formulations are significantly more effective than the free drugs. (Note the abstract, Materials and Methods and results). Vaage in addition teaches that a number of studies in animal models have shown that the therapeutic activities of anti-cancer drugs can be increased and prolonged and toxic effects reduced when they are encapsulated in liposomes (page 959, col. 1).

Saxon discloses compositions containing two cancer drugs encapsulated in liposomes. The drugs taught are vincristine and mitoxantrone. The diameter of the liposomes is between 100-120 nm. (Abstract and Materials and Methods).

Bally teaches that two antineoplastic agents can be co encapsulated within the liposomes (col. 15). The drugs taught include fluorouracil, cisplatin, doxorubicin, vincristine, vinblastine and others (col. 7).

Encapsulation of cisplatin-taxane combination taught by Englom, or carboplatin-several other anti-cancer drugs taught by Kano or Irinotecan drug combinations of Guichard would have been obvious to one of ordinary skill in the art, with a reasonable

Art Unit: 1612

expectation of success because the references of Saxon, and Bally each teach the knowledge in the art of encapsulation of both agents in liposomes or because of the advantages of liposomes such as reduced toxicity taught by Vaage. The use of art known algorithms and analysis of the data such as Chou-Talalay median-effect method to determine the non-antagonist ratio with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since they are known to be practiced in the art.

5. Claims 42-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Englom (British Journal of Cancer, 79 (2), 1999) or Kano (leukemia Research, vol. 17, 1993) or Guichard (Biochemical Pharmacology, vol. 55, 1998) in combination with applicant's statements of prior art record, in further combination with Vaage, Saxon (Journal of Liposome Research) Bally (5,736,155) individually or in combination as set forth above, further in view of Giles (US2003/0083316).

The teachings of Engblom, Kano, Guichard, applicant's statements of prior art, Vaage, Saxon have been discussed above.

Giles while disclosing a pharmaceutical combination for the treatment of cancer using OddC and Ara-C teaches first determination of the effect of the combination in CRRF_CEM cells. To determine if the combination is additive, antagonistic or synergistic, a linear cure fitting was used, using the CalcuSyn software which is based on algorithms developed by Chou and Talalay (Examples, Example 3 in particular).

Art Unit: 1612

The use of art known algorithms and analysis of the data such as Chou-Talalay median-effect method to determine the non-antagonist ratio with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since the reference of Giles shows that this method is used to determine the effect is additive, antagonistic or synergistic.

6. Claims 42-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuo (Journal of controlled Release, 2001) or Krishna (Int. J. Cancer, 2000) or Singh (European Journal of Pharmaceutics and Biopharmaceutics, 2001) or Sadasivan (Cancer Letters, 1991) by themselves or in combination (all are of record) in combination with applicant's statements of prior art record or vice versa.

According to instant claims liposomes have stably associated with first antineoplastic agent and a drug resistance-modulating agent which have amounts which have a synergistic effect. Instant claims do not define what the drug resistance modulating agent is.

Matsuo teaches a method of preparation of liposomes which reverse multi-drug resistance. The liposomes contain vincristine and MRK-16, a monoclonal antibody to P-glycoprotein (see abstract and materials and methods). What is lacking in Matsuo is the teaching of first determining the amounts of vincristine and MRK-16 which are synergistic by an in vitro by Chow-Talalay median effect method and then use those amounts of the active agents in the liposomes.

Krishna teaches increased intracellular drug accumulation and complete chemo sensitization in multidrug-resistant solid tumors by co-administering valsphor (PSC

Art Unit: 1612

833) with sterically stabilized liposomal doxorubicin (abstract and materials and methods).

Singh discloses the preparation of stealth monensin immunoliposomes as potentiators of immunotoxins (abstract and materials and methods).

Sadasivan teaches a method of preparation of composition which contains verapamil and liposome encapsulated doxorubicin for the reversal of multi-drug resistance (summary and materials and methods).

Applicant on pages 17 and 18 states that various algorithm methods, Chou-Talalay median effect method to determine the synergistic activity of anti-cancer drugs is known in the art.

Assuming that the amounts of the active agents in Matsuo, Krishna, Singh and Sadasivan are not synergistic, it is deemed obvious to one of ordinary skill in the art to prepare Matsuo's liposomes with amounts of the active agents in synergistic amounts by first determining the synergistic amounts in vitro with a reasonable expectation of success since in vitro determination of the synergistic amounts is well-known in the art as stated by applicant.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

Art Unit: 1612

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 42-46 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14, 16-17, 22-23 and 26-27 of copending Application No. 11/304,328. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims in both applications are drawn to the same method of preparation of active agent containing liposomes. Claims in instant application recite however a combination of first neoplastic agent and a drug resistance modulating agent as opposed to 'first antineoplastic agent and 'second antineoplastic agent' in the claims of the copending application. Since a drug resistance modulating agent can be another anti-neoplastic agent with an activity of its own or potentiate the effect of the antineoplastic agent (see specification page 10), the terms are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S. KISHORE whose telephone number is

Art Unit: 1612

(571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK